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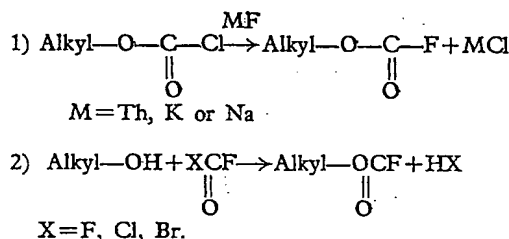


(54) FLUOROFORMATES

(71) We, FARBENFABRIKEN BAYER AKTIENGESELLSCHAFT, a body corporate organised under the laws of Germany of 509, Leverkusen, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a process for the production of alkyl fluoroformates. 10

Fluoroformates which contain primary and secondary alkyl groups are known from the literature and can be prepared by two different processes: 15



The preparation of fluoroformic acid esters by the exchange of Cl by F as shown in equation 1) is only applicable to a limited number of esters. Since the exchange reaction generally requires elevated reaction temperatures, only those chloroformates which are stable when heated can be used in this reaction. 20

Tertiary alkyl esters of fluoroformic acid have been disclosed in Belgian Patent Specification No. 708,452 and can be prepared by the process shown in equation 2) under certain conditions. 25

The processes illustrated by equation 2) which have so far been described have, however, a serious disadvantage for industrial application. This is that the reaction must be started at low temperatures of about -70°C . and must then be continued over a wide temperature range of up to room temperature or, in the case of sensitive types of esters, temperatures of up to about 0°C . Both the attainment of the low starting temperatures 30

and the increase of temperature over a wide temperature range is technically very expensive and makes it difficult to carry out the process continuously. Even if the necessary reaction conditions are obtained for these difficult preparations, it is not possible to prevent the formation of the corresponding neutral carbonates in addition to the required fluoroformates when COFCl is used as starting material (J. Chem. Soc. 1948, 2186). The yields in this process are therefore in the region of 50 to 55% of the theoretical. For this reason, COFBr has been suggested as starting material in J. Org. Chem 21, 1391 (1956). A more highly selective reaction with the alcohols can thus be achieved due to the greater differences in the reactivity of the two halogen atoms, and the yields can therefore be increased by about 20% of the theoretical yield. However this reagent is not suitable for industrial use as it is difficultly accessible. Accordingly to U.S. Patent Specification No. 3,362,980, the undesired formation of car- 45 50 55 60

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bonates in the preparation of fluoroformates of vicinal polyhydric alcohols is suppressed by using tertiary amines as catalysts. However, the reaction takes a very long time (40 hours in the example). This process is therefore also not suitable for industrial application.

The present invention provides a process for the preparation of alkyl or cycloalkyl fluoroformates from aliphatic or cycloaliphatic alcohols and COFCl and/or COF_2 in the presence of at least an equivalent quantity of isobutylene in which the components are reacted together at temperatures of -20 to $+80^\circ \text{C}$. under a pressure of 0.1 to 50 excess atmospheres, preferably of up to 20 excess atmospheres.

It is necessary to work in a pressure vessel. The excess pressure required may either be the pressure of the mixture at the temperature employed or it may be increased by forcing in an inert gas (nitrogen).

When the reaction is carried out in this way, it proceeds very rapidly so that a continuous process becomes possible. Considerable increase in the rate and simplification in the method of preparing fluoroformates is achieved by the process according to the invention. Moreover, it was not to be expected from the state of the art mentioned above that it would be possible to carry out the process with high yields under the conditions employed according to the invention.

The aliphatic or cycloaliphatic alcohols which may be used for carrying out the process may be primary, secondary or, preferably tertiary aliphatic alcohols, in particular alkyl alcohols containing 1 to 6 carbon atoms in the alkyl group. The term alkyl also includes cycloalkyl. Methyl alcohol, cyclohexyl alcohol, n-butyl alcohol and, in particular, tertiary butyl alcohol are particularly suitable representatives.

The COFCl or COF_2 used as starting material is obtained by known processes from phosgene and SbF_3 . These processes always result in a mixture of COF_2 , COFCl and unchanged COCl_2 . The components can be obtained pure by distillation, but it is one advantage of the process according to the invention that the crude mixture obtained from this process may be used directly, provided only that the correct amount of COFCl and COF_2 is present.

The process is generally carried out by introducing the alcohol and isobutylene into a pressure vessel in which the temperature should be maintained in the region of 0°C ., and then forcing in COFCl and/or COF_2 , i.e. in general a mixture of fluorinated phosgenes. When the reaction is complete, the pressure in the autoclave is released. The reaction product can be used directly after concentration by evaporation in a slight vacuum. It contains as impurities mainly the chlorides e.g. t-butylchloride of the alcohols on which the

reaction is based. The fluoroformate can be isolated from the reaction product by distillation.

If the process is carried out continuously, all the starting materials are pumped continuously into a pressure vessel and are then removed after the reaction. In a special method of carrying out the process continuously, the reaction product is transferred into a vacuum via an intermediate vessel. The crude product obtained in this way can be used without further purification.

The molar ratios of aliphatic alcohol and fluorinated phosgene used as starting materials are not very important for the process. Preferably approximately molar ratios should be used to start with. For reasons of cost, it may be desirable to use the acylating component in excess. Isobutylene, which serves here both as a solvent and as an HCl acceptor, may be used in excess amounting to as much as three times and preferably $1\frac{1}{2}$ times the calculated quantity.

Alkyl fluoroformates are important peptide reagents.

The process is illustrated by the following Examples.

EXAMPLE 1

A solution of 150 g of tertiary butanol and 188 g of isobutylene is introduced into a stainless steel autoclave of 1.3 litres capacity. 287 g of a mixture of fluorinated phosgenes which contain 70 mols % of COF_2 and COFCl are introduced under pressure in 20 minutes at a temperature of 0°C . which is maintained by external cooling. The autoclave contents are then heated to 10°C , which causes the pressure to rise to 4 excess atmospheres approximately although the pressure rapidly diminishes again to about 0.5 atmospheres. The pressure is released and the residue is concentrated to 247 g by evaporation under a slight vacuum. The residue then has an $n_D^{20} = 1.3642$, and according to gas chromatographic analysis it contains 28.5% mol of tertiary butyl chloride and 68.0% mol = 76.3% by weight of F-formic acid tertiary butyl ester.

This corresponds to a yield of 78.2% of theory, based on the tertiary butanol used.

This crude product can be used directly as an acylating component for introducing protective groups in peptide syntheses.

However, the pure tertiary butyl fluoroformate can be easily obtained from the crude product by distillation as a liquid of b.p._{24 mm} = $9-12^\circ \text{C}$ and a refractive index $n_D^{20} = 1.3586$.

EXAMPLE 2

Cyclohexyl fluoroformate, of b.p._{12 mm} = 45°C , $n_D^{20} = 1.4160$ is obtained in a yield of 72% in a manner analogous to Example 1, using cyclohexanol as starting material.

EXAMPLE 3

Methyl fluoroformate, of b.p. 35—42° C. and $n_D^{20}=1.3540$, is obtained in 90% yield by a method analogous to Example 1, using 5 methanol as starting material.

EXAMPLE 4

2200 G of molten tertiary butanol is sucked into an evacuated pressure flask. 3200 ml of isobutylene is then forced into the tertiary butanol by means of excess nitrogen pressure. 10 A homogeneous solution is obtained in the flask by repeated shaking. This mixture contains 0.495 mol of tertiary butanol per 100 ml. The reaction vessel used is a 0.3 litres 15 autoclave of V4A steel equipped with stirrer and circulating external cooling. Two inlet tubes lead directly to the stirrer blade via valves. An overflow tube starts 2 cm below the lid. 660 ml per hour of the butanol solution 20 are pumped through an inspection vessel and one of the inlet tubes into this autoclave at an external cooling of -2° C. Fluorinated phosphene is dosed from a second inspection vessel by means of a membrane pump at the same 25 time. A fluorophosgene mixture of the following composition was used: 9% COF_2 , 43.7% COCIF and 46.2% COCl_2 (density = approximately 1.1). It was pumped in at the rate of 300 ml per hour. The pressure is 30 allowed to rise up to 18 excess atmospheres in the 0.3 litre autoclave and is then released into a container equipped with a stirrer via the overflow tube at the same rate as that at which it is pumped into the autoclave. This 35 container is equipped with a jacket which is maintained at a temperature of +10° C with water. The gaseous products escape from the top of this container and are carried to a washing plant. If the external cooling is maintained at the temperature indicated above, the 40 temperature of the contents in the reaction autoclave rises at the most to +2° C. The reaction product can be removed from the low pressure container via an ascending tube if 45 the gas discharge tube is closed for a short time. This does not interrupt the process of pumping in the components. If the operation

is continued for a total of 6 hours, several samples of the reaction product provide an approximately 70% yield of the tertiary butyl fluoroformate, based on the sum of COF_2 and COCIF used. 50

WHAT WE CLAIM IS:—

1. A process for the preparation of alkyl or cycloalkyl fluoroformates from aliphatic or cycloaliphatic alcohols and COFCl and/or COF_2 in the presence of at least an equivalent quantity of isobutylene, in which the components are reacted together at temperatures of -20 to +80° C. under a pressure of 0.1 to 50 excess atmospheres. 55
2. A process as claimed in claim 1 in which the pressure used is up to 20 excess atmospheres.
3. A process as claimed in claim 1 or claim 2 in which the aliphatic alcohol used is a tertiary alcohol. 65
4. A process as claimed in any of claims 1 to 3 which is carried out at approximately 0° C. 70
5. A process as claimed in any of claims 1 to 4 in which $1\frac{1}{2}$ times the calculated quantity of isobutylene is used.
6. A process as claimed in any of claims 1 to 5 in which the components are reacted together continuously by pumping them into a pressure vessel. 75
7. A process as claimed in claim 6 in which the reaction product is continuously released into a vacuum via an intermediate vessel. 80
8. A process as claimed in claim 1 substantially as herein described with reference to any one of the Examples.
9. Alkyl fluoroformates when prepared by a process as claimed in any of claims 1 to 8. 85

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